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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/734,070	12/11/2003	Stephen M. Zappala	16865-00012	1261

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EXAMINER
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JAGOE, DONNA A

ART UNIT	PAPER NUMBER
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1614

DATE MAILED: 03/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/734,070	ZAPPALA, STEPHEN M.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Donna Jagoe	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-34 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-34 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>12/11/03</u> . | 6) <input type="checkbox"/> Other: ____.  |

## **DETAILED ACTION**

***Claims 1-34 are presented for reexamination.***

### ***Priority***

Applicant's claim for domestic priority under 35 U.S.C. 120 is acknowledged. However, it is noted that the provisional application and U.S. Application upon which priority is claimed fails to provide adequate support for claims 1-2 and 4-34 of this application. The only portion that provides support is the paragraph in column 4, lines 50 to 60, which recites the administration of 10 cc of 0.25% bupivacaine, combined with 20 cc of 1% lidocaine for a total volume of 30 cc. Claims 1-2 and 4-34 are not commensurate in scope with the priority document.

### ***Claim Objections***

1. Claim 9 is objected to because of the following informalities: the word lidocaine in line 2 of the claim is misspelled. Appropriate correction is required.
2. Claim 9 is objected to because of the following informalities: the word bupivacaine in line 3 of the claim is misspelled. Appropriate correction is required.
3. Claim 29 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. Claim 29, drawn to the anesthetic of claim 28 wherein said combination comprises a mixture of lidocaine and

Art Unit: 1614

bupivacaine in a ratio of less than 10:1. Claim 28, from which it depends is drawn to the combination of **1% lidocaine hydrochloride** and **0.25% bupivacaine hydrochloride**.

Amending the claim to recite "the anesthetic of claim 28 wherein said combination comprises a mixture of 1% lidocaine hydrochloride and 0.25% bupivacaine hydrochloride in a ratio of less than 10:1" would obviate the objection to the claim.

4. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Please note that there are two claims numbered as claim 25. Misnumbered claim 25-33 been renumbered 26-34.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9 and 31-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See

Art Unit: 1614

MPEP § 2172.01. The omitted steps are: applicant claims a method of reducing perioperative pain comprising the steps of providing a sterile isotonic pharmacology agent comprising lidocaine and bupivacaine in a ratio of less than or equal to 10:1 and **introducing** said agent as an adjunct for preemptive analgesia before a surgical procedure is initiated. The step missing is administration of said agent. It is not clear to the examiner what is meant by the term "**introducing**" said agent.

Claims 31-34 recites the limitation "**the anesthetic** of claim 17" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim because claim 17 is drawn to a **method** for administering local or regional anesthesia.

### ***Protest***

Applicants' attention is drawn to the protest entered into this reissue case on 22 November 2004. The following rejections are adopted from the protest.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

Art Unit: 1614

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-8 and 16-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seow et al., Miller Goodman and Gilman(U) and Cousins.

The claims are drawn to a compositions and methods of reducing perioperative pain comprising administering lidocaine and bupivacaine and optionally a buffer and a vasoconstrictor in a ratio of less than or equal to 10:1. The agent is capable of providing analgesic effect for at least 6 hours and is administered as an injectable therapy selected from subcutaneous, caudal, epidural, intramuscular, intradural, intraspinous, and peripheral nerve blockade.

Seow et al. teach administration of 2% lidocaine and 0.5% bupivacaine in a mixture for epidural blockade in ratios of from 3:1 to 1:3 which overlaps and encompasses the claimed ranges. Further, regarding the claims ranges of less than 10:1, one skilled in the art would have been motivated to prepare additional useful compositions of the ranges taught by the prior art. While the reference is silent regarding some % ratios, the difference in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. When the general conditions are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. In re Aller, 220 F.2d 45, 105 USPQ 233, 235 (CCPA 1955). In absence of any criticality and/or unexpected results of the additional ranges claimed,

Art Unit: 1614

instant invention is considered obvious. The anesthetic agents contained 1:200,000 epinephrine (a vasoconstrictor) (see abstract).

Duration of action of the lidocaine and bupivacaine is  $286 \pm 32$  minutes (see Seow abstract). This differs from the claimed "at least 6 hours" however, Goodman and Gilman teaches the duration of action and peak concentrations of local anesthetics in blood depends upon the amount injected, the physical characteristics of the local anesthetic and whether epinephrine is used. They are also determined by the rate of blood flow to the site of injection (page 313, column 1). By adding epinephrine, the duration can be approximately doubled by decreasing the rate of absorption of drug into the blood stream (see page 311, columns 1-2). Further, Goodman and Gilman teaches that Goodman and Gilman teach that the latency of the anesthetic effect of lidocaine injected about the ulnar nerve is 3 minutes, but this value is nearly 15 minutes when the drug is injected about the brachial plexus (page 312, column 2) so it also depends on the site of administration. Goodman and Gilman teach the duration of action of bupivacaine is 400 to 450 minutes and the duration of action of lidocaine is 60 to 120 minutes (page 312, column 2). Thus it would have been obvious to one of ordinary skill in the art to vary the aliquot of lidocaine to bupivacaine and to add or exclude epinephrine to increase or decrease the duration of action of the anesthetic motivated by the teachings of Goodman and Gilman as described above and in Chapter 15 of the Pharmacologic Basis of Therapeutics.

Seow does not teach the combination of 1% lidocaine and 0.25% bupivacaine, however, Miller discloses that to create an epidural blockade, the "usual concentration"

Art Unit: 1614

range for lidocaine is 1-2% and the "usual concentration" range for bupivacaine is 0.25% to 0.75% (page 506, table 15-7). It would have been made obvious to one of ordinary skill in art at the time it was made to create a rapid-onset, long acting anesthetic motivated by the teaching of Seow et al. who teach lidocaine-bupivacaine combination and the teachings of Miller wherein the concentrations of lidocaine and bupivacaine are selected from the range of usual concentrations.

Goodman and Gilman further teach that in practice, local anesthetics such as lidocaine, which act rapidly but relatively briefly, are **often** combined with an anesthetic such as bupivacaine, which although slow in onset, has a long duration of action.

Cousins provides the motivation to buffer the anesthetic solution wherein it is disclosed that sodium bicarbonate will increase the pH of the local anesthetic solution, which in turn will increase the amount of the drug in the uncharged base form. Thus the rate of diffusion across the nerve sheath and nerve membranes should be enhanced resulting in a more rapid onset of anesthesia. Sodium bicarbonate was added to bupivacaine resulting in a significant decrease in the latency of brachial plexus blockade and it is reported that the duration of anesthesia was prolonged by increasing the pH of the local anesthetic solution (page 105, column 1, first paragraph). It does not teach the specific buffers sodium hydroxide and hydrochloric acid, however, the net effect would be the same by the addition of the buffers sodium hydroxide and hydrochloric acid, an increase to the pH to 7.4. Additional motivation is provided for the pH of 7.4 because that is the normal pH of human blood and spinal fluid. It would have been obvious to

Art Unit: 1614

buffer to a pH of 7.4 motivated by the desire for a faster latency period and longer duration of action as disclosed by Cousins.

2. Claims 9-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seow et al., Miller, Goodman and Gilman(U) and Cousins as applied to claims 1-8 and 16-34 above, and further in view of Ko et al.

Ko et al. teach a method for reducing perioperative pain by injecting a preemptive analgesic solution before incision, wherein the preemptive analgesic used is a 1:1 mixture of 1% lidocaine and 0.5% bupivacaine (page 875). The preincisional injection technique of Ko is infiltration into the dermis and subcutaneous tissues (page 875, column 2, line 1). Although the concentration of Ko et al. was 1% lidocaine and 0.5% bupivacaine HCl, it is disclosed that there may be an advantage to using a larger volume of more diluted anesthetic agents, by diluting the concentration of local anesthetic agents, greater volumes can be used. Greater volumes would be more effective than smaller volumes of more concentrated agents because a larger tissue area may be anesthetized. It would have been made obvious to one of ordinary skill in art at the time it was made to employ a more dilute solution of bupivacaine in the mixture of lidocaine and bupivacaine. Such a modification would have been motivated by the reasoned expectation of producing an anesthetic composition which is effective in comprehensively producing preemptive anesthesia to greater areas of tissue in a patient as recited by Ko et al. above.

In holding an invention obvious in view of a combination of references, there must be some suggestion, motivation or teaching in the prior art that would have led a person of ordinary skill in the art to select the references and combine them in the way that would produce the claimed invention. This motivation may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. Here, filtered through the knowledge of one skilled in the art, the prior art disclosed that lidocaine is available in a concentration of 1% and bupivacaine is available in a concentration of 0.25% and both are available with epinephrine 1:200,000. It is also disclosed in the prior art that lidocaine has a short duration of action and short latency period and bupivacaine has a longer duration of action and a longer latency period. The prior art teaches that these agents are frequently combined because a shorter latency period and longer duration of action is desired in some surgical procedures. It is further disclosed by the prior art that bupivacaine has a duration of action of about 400 to 450 minutes (at least 6 hours). In addition, by the time of the claimed invention, lidocaine and bupivacaine were well-known and successful local anesthetic agents, and were frequently combined. Accordingly, there was clear motivation to combine the lidocaine and bupivacaine to produce a shorter latency period and longer duration of action.

Thus the claims fail to patentably distinguish over the state of the art as represented by the cited references.

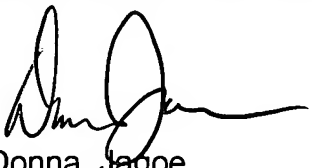
Accordingly, for the above reasons, the claims are deemed properly rejected and none are allowed.

### **Correspondence**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-0576. The examiner can normally be reached on Monday through Thursday from 9:00 A.M. - 3:00 P.M..


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Donna Jagoe  
Patent Examiner  
Art Unit 1614

02/14/2005



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